Hypertriglyceridemia: A strategic approach

This review, and the at-a-glance tables that follow, detail indications and strategies for the treatment of adults with hypertriglyceridemia.

CASE 1

Tyler M, age 40, otherwise healthy, and with a body mass index (BMI) of 30, presents to your office for his annual physical examination. He does not have a history of alcohol or tobacco use.

Mr. M’s obesity raises concern about metabolic syndrome, which warrants evaluation for hypertriglyceridemia (HTG). You offer him lipid testing to estimate his risk of atherosclerotic cardiovascular disease (ASCVD).

The only abnormal value on the lipid panel is a triglyceride (TG) level of 264 mg/dL (normal, < 175 mg/dL). Mr. M’s 10-yr ASCVD risk is determined to be < 5%.

What, if any, intervention would be triggered by the finding of moderate HTG?

CASE 2

Alicia F, age 30, with a BMI of 28 and ASCVD risk < 7.5%, comes to the clinic for evaluation of anxiety and insomnia. She reports eating a high-carbohydrate diet and drinking 3 to 5 alcoholic beverages nightly to help her sleep.

Ms. F’s daily alcohol use prompts evaluation for HTG. Results show a TG level of 1300 mg/dL and a high-density lipoprotein (HDL) level of 25 mg/dL (healthy HDL levels: adult females, ≥ 50 mg/dL; adult males, ≥ 40 mg/dL). Other test results are normal, except for elevated transaminase levels (just under twice normal).

What, if any, action would be prompted by the patient’s severe HTG and below-normal HDL level?

How HTG is defined: Causes, cutoffs, signs

HTG is most commonly caused by obesity and a sedentary lifestyle; certain associated comorbid medical conditions can also be a precipitant (TABLE 1). Because the condition is a result of polygenic phenotypic expression, even a genetically low-risk
patient can present with HTG when exposed to certain medical conditions and environmental causes.

Primary HTG (genetic or familial) is rare. Genetic testing may be considered for patients with TG > 1000 mg/dL (severely elevated TG = 500 to 1999 mg/dL, measured in fasting state\(^*\)) or a family history of early ASCVD (TABLE 1,2,3). Typically, HTG is asymptomatic. Xanthelasmas, xanthomas, and lipemia retinalis are found in hereditary disorders of elevated TGs. Occasionally, HTG manifests as chylo-micronemia syndrome, characterized by recurrent abdominal pain, nausea, vomiting, and, in severe HTG, pancreatitis.3

Fine points of TG measurement

Triglycerides are a component of a complete lipid profile, which also includes total cholesterol, calculated low-density lipoprotein (LDL-C), and HDL.4 As in both case vignettes, detection of HTG is often incidental, when a lipid profile is ordered to evaluate the risk of ASCVD. (Of note, for people older than 20 years, the US Preventive Services Task Force no longer addresses the question, “Which population should be screened for dyslipidemia?” Instead, current recommendations answer the question, “For which population should statin therapy be prescribed?”5)

Effect on ASCVD risk assessment. TG levels are known to vary, depending on fasting or nonfasting status, with lower levels reported when fasting. An elevated TG level can lead to inaccurate calculation of LDL when using the Friedewald formula6:

\[
\text{LDL} = \text{total cholesterol} - \left(\frac{\text{triglycerides}}{5}\right) - \text{HDL}
\]

The purpose of testing lipids in a fasting state (> 9 hours) is to minimize the effects of an elevated TG level on the calculated LDL. In severe HTG, beta-quantitation by ultracentrifugation and electrophoresis can be performed to determine the LDL level directly.

Advantage of nonfasting measurement. When LDL-C is not a concern, there is, in fact, value in measuring TGs in the nonfasting state. Why? Because a nonfasting TG level

\(^*\)In comparison, a normal level of triglycerides is < 175 mg/dL; a moderately elevated level, measured in a fasting or nonfasting state, 175-499 mg/dL; and a very severely elevated level, ≥ 2000 mg/dL.
Studies have found a higher ASCVD risk in the setting of an elevated postprandial triglyceride level accompanied by a low HDL level.

The Copenhagen City Heart Study identified postprandial HTG as an independent risk factor for atherogenicity, even in the setting of a normal fasting TG level.7 American Association of Clinical Endocrinologists and American College of Endocrinology guidelines endorse testing the nonfasting TG level when the fasting TG level is elevated in a lipid profile; if the nonfasting TG level is > 500 mg/dL, evaluation for secondary causes is warranted9,10 (TABLE 1).

In a practical sense, therefore, offering patients nonfasting lipid testing allows more people to obtain access to timely care.

Pancreatitis. Acute pancreatitis commonly prompts an evaluation for HTG. The risk of acute pancreatitis in the general population is 0.04%, but that risk increases to 8% to 31% for a person with HTG.11 Incidence when the TG level is > 500 mg/dL is thought to be increased because chylomicrons, acting as a TG carrier in the bloodstream, are responsible for pancreatitis.7 Treating HTG can reduce both the risk and recurrence of pancreatitis12,13; given that the postprandial TG level can change rapidly from severe to very severe (> 2000 mg/dL), multiple guidelines recommend pharmacotherapy to a TG goal of < 500-1000 mg/dL.1,9,13,14

An ASCVD risk–HTG connection? In the population already at higher risk of ASCVD (> 7.5%), HTG is recognized as a risk-enhancing factor because of its atherogenic potential (TABLE 2); however, there is insufficient evidence that TGs have a role as an independent risk factor for ASCVD. In a population-based study of 58,000 people, 40 to 65 years of age, conducted at Copenhagen [Denmark] University Hospital, investigators found that those who did not meet criteria for statin treatment and who had a TG level > 264 mg/dL had a 10-year risk of a major adverse cardiovascular event similar to that of people who did meet criteria for statin therapy.15

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes)
studies, among others, have failed to show a significant reduction in coronary events by treating HTG.\textsuperscript{10} That said, it’s worth considering the findings of other trials:

- In the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, an overall 28% reduction in endpoint events (myocardial infarction, acute coronary syndrome) was seen with high-intensity statin therapy, compared to moderate-intensity therapy.\textsuperscript{10} However, there was a sizeable residual risk identified that was theorized by investigators to be associated with high non-HDL lipoproteins, including TGs.
- A 2016 study in Israel, in which 22 years of data on 15,355 patients with established ASCVD were studied, revealed that elevated TGs are associated with an increased long-term mortality risk that is independent of the HDL level.\textsuperscript{16}
- A cross-sectional study, nested in the prospective Copenhagen City Heart Study, demonstrated that HTG is associated with an increase in ischemic stroke events.\textsuperscript{17}

**Treatment**

**Therapeutic lifestyle changes**

Changes in lifestyle are the foundation of management of, and recommended first-line treatment for, all patients with HTG. Patients with a moderately elevated TG level (175-499 mg/dL, measured in a fasting or nonfasting state) can be treated with therapeutic lifestyle changes alone\textsuperscript{1,2}; a trial of 3 to 6 months (see specific interventions below) is recommended before considering adding medications.\textsuperscript{10}

### Weight loss

There is a strong association between BMI > 30 and HTG. Visceral adiposity is a much more significant risk than subcutaneous adipose tissue. Although weight loss to an ideal range is recommended, even a 10% to 15% reduction in an obese patient can reduce the TG level by 20%. A combination of moderate-intensity exercise and healthy eating habits appears to assist best with this intervention.\textsuperscript{18}

### Exercise

Thirty minutes a day of moderate-intensity exercise is associated with a significant drop in postprandial TG. This

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**TABLE 2**

Risk factors and risk-enhancing factors for atherosclerotic cardiovascular disease\textsuperscript{2}

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Risk-enhancing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td></td>
</tr>
<tr>
<td>- Men &gt; 45 y</td>
<td></td>
</tr>
<tr>
<td>- Women &gt; 55 y</td>
<td></td>
</tr>
<tr>
<td>• Male gender</td>
<td></td>
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<tr>
<td>• Race (eg, African American)</td>
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</tr>
<tr>
<td>• Diabetes</td>
<td></td>
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<tr>
<td>• Hypertension</td>
<td></td>
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<tr>
<td>• Prior cardiovascular event</td>
<td></td>
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<tr>
<td>• Smoking</td>
<td></td>
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<tr>
<td>• Elevated level of low-density lipoprotein</td>
<td></td>
</tr>
<tr>
<td>• Low (&lt; 40 mg/dL) level of high-density lipoprotein</td>
<td></td>
</tr>
<tr>
<td>• Stages 3 and 4 chronic kidney disease\textsuperscript{*}</td>
<td></td>
</tr>
<tr>
<td>• Polycystic ovary syndrome\textsuperscript{*}</td>
<td></td>
</tr>
<tr>
<td>• Evidence of coronary artery calcification\textsuperscript{*}</td>
<td></td>
</tr>
<tr>
<td>• Parental history of cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>• Family history of stroke</td>
<td></td>
</tr>
<tr>
<td>• Metabolic syndrome, with or without diabetes</td>
<td></td>
</tr>
<tr>
<td>• Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td>• Inflammatory disorder</td>
<td></td>
</tr>
<tr>
<td>• Hypertriglyceridemia</td>
<td></td>
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<tr>
<td>• Ankle–brachial index &lt; 0.9</td>
<td></td>
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<tr>
<td>• Elevated level of C-reactive protein (on high-sensitivity testing)</td>
<td></td>
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<tr>
<td>• Elevated levels of lipoproteins and apolipoprotein B</td>
<td></td>
</tr>
<tr>
<td>• Early menopause</td>
<td></td>
</tr>
<tr>
<td>• Preeclampsia</td>
<td></td>
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<tr>
<td>• High-risk ethnic group (eg, South Asian)</td>
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</tr>
</tbody>
</table>

\textsuperscript{*}Newly identified risk factor.
benefit can last as long as 3 days, suggesting a goal of at least 3 days a week of an active lifestyle. Such a program can include intermittent aerobics or mild resistance exercise.19

Healthy eating habits. The difference between a low-fat, high-carbohydrate diet and a high-fat, low-carbohydrate diet is less important than the overall benefit of weight loss from either of these diets. Complex carbohydrates are recommended over simple carbohydrates. A low-carbohydrate diet in a patient with diabetes has been demonstrated to improve the TG level, irrespective of weight change.20

A Mediterranean diet can reduce the TG level by 10% to 15%, and is recommended over a low-fat diet.14 (This diet generally includes a high intake of extra virgin olive oil; leafy green vegetables, fruits, cereals, nuts, and legumes; moderate intake of fish and other meat, dairy products, and red wine; and low intake of eggs and sugars.) The American Heart Association recommends 2 servings of fatty fish a week for its omega-3 oil benefit of reducing ASCVD risk. Working with a registered dietician to assist with lipid lowering can produce better results than physician-only instruction on healthy eating.9

Alcohol consumption. Complete cessation or moderation of alcohol consumption (1 drink a day/women and 2 drinks a day/men*) can produce better results than physician-only instruction on healthy eating.3

*One “standard” alcoholic drink is considered to contain approximately 0.16 fluid ounces (14 g) of pure alcohol; however, the amount of alcohol in any drink can vary widely.21

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**TABLE 3**

*Agents in your arsenal to treat hypertriglyceridemia*4,13,18,23

<table>
<thead>
<tr>
<th>Class or name of medication</th>
<th>Mechanism of action</th>
<th>Reduction in TG level</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Increase lipoprotein lipase activity to clear TG from plasma</td>
<td>10%-15%</td>
<td>Dizziness&lt;br&gt;Tachycardia&lt;br&gt;Myalgia&lt;br&gt;Elevated LFT</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Inhibit secretion of TG from liver and reduce blood TG levels&lt;br&gt;Activate lipoprotein lipase to stimulate clearance of TG from plasma</td>
<td>30%-50%</td>
<td>Dyspepsia&lt;br&gt;Gallstones&lt;br&gt;Myopathy</td>
</tr>
<tr>
<td>Omega-3 ethyl esters</td>
<td>Same as for fibrates (see above)</td>
<td>20%-50%</td>
<td>Fishy taste&lt;br&gt;Burping&lt;br&gt;Bleeding diathesis&lt;br&gt;Hyperglycemia</td>
</tr>
<tr>
<td>Ezetimibe&lt;sup&gt;23,a&lt;/sup&gt;</td>
<td>Decreases cholesterol absorption from small intestine</td>
<td>5%-10%&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Bloating&lt;br&gt;Abnormal bleeding&lt;br&gt;Constipation</td>
</tr>
<tr>
<td>Niacin</td>
<td>Blocks release of free fatty acid from adipose tissue&lt;br&gt;Reduces rate of secretion of very-low-density lipoprotein particles</td>
<td>10%-30%</td>
<td>Elevated LFT&lt;br&gt;Flushing&lt;br&gt;Gout&lt;br&gt;Hyperglycemia&lt;br&gt;Macular edema&lt;br&gt;Peptic ulcer disease</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFT, liver function tests; TG, triglycerides.

<sup>a</sup>Indicated, in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL, apolipoprotein B, and non-HDL cholesterol in patients with mixed hyperlipidemia.18,23
is recommended to improve HTG. Among secondary factors, alcohol is commonly the cause of an unusually high elevation of the TG level.14

**Smoking cessation.** Smoking increases the postprandial TG level.10 Complete cessation for just 1 year can reduce a person’s ASCVD risk by approximately 50%. However, in a clinical trial,22 smoking cessation did not significantly decrease the TG level—possibly because of the counterbalancing effect of weight gain following cessation.

**Medical therapy**

In addition to lifestyle modification, medications are recommended to reduce atherogenic potential in patients with moderate or severe HTG and an ASCVD risk > 7.5% (TABLE 313,14,23 and TABLE 413,19). Before initiating medical therapy, we recommend that you engage in shared decision-making with patients to (1) delineate treatment goals and (2) describe the risks and benefits of medications for HTG.2

**Statins.** These agents are recommended first-line therapy for reducing ASCVD risk.2 If the TG level remains elevated (> 500 mg/dL) after statin therapy is maximized, an additional agent can be added—ie, a fibrate or fish oil (see below).

**Fibrates.** If a fibrate is used as an add-on to a statin, fenofibrate is preferred over gemfibrozil because it presents less risk of the severe myopathy that can develop when taken with a statin.13 Despite the effectiveness of fibrates in reducing the TG level, these drugs have not been shown to reduce overall mortality.24 The evidence on improved cardiovascular outcomes is subgroup-specific (ie, prevention of a second myocardial infarction in the setting of optimal statin use and elevated non-HDL lipoproteins).12 A study demonstrated that gemfibrozil reduced the incidence of transient ischemic attack and stroke in a subgroup of male US veterans who had coronary artery disease and a low HDL level.25

**Fish oil.** The omega-3 ethyl esters eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), available as EPA alone or in combination with DHA, do not interact with statins and are tolerated well. They reduce

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**TABLE 4**

<p>| Strategies for when and how to treat HTG in adults2,9 |
| --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>Severity</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients &gt; 20 y</td>
<td>Moderate HTG; risk of ASCVD &lt; 7.5%</td>
<td>Therapeutic lifestyle changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Management of secondary causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consideration of the role of medications that can contribute to HTG</td>
</tr>
<tr>
<td>40-75 y</td>
<td>Moderate HTG; risk of ASCVD ≥ 7.5%</td>
<td>Therapeutic lifestyle changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Management of secondary causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiation (or intensification) of statin therapy</td>
</tr>
<tr>
<td>All patients &gt; 20 y</td>
<td>Severe HTG; risk of ASCVD &lt; 7.5%</td>
<td>Therapeutic lifestyle changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evaluation and management of primary and secondary causes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrate therapy</td>
</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td>Fibrate therapy</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; HTG, hypertriglyceridemia.

175-499 mg/dL, measured in a fasting or nonfasting state.

≥ 500 mg/dL, measured in a fasting or nonfasting state.

The risk of acute pancreatitis in the general population is 0.04%, but that risk increases to 8% to 31% for a person with hypertriglyceridemia.
There is a strong association between a BMI > 30 and hypertriglyceridemia.

Hypertriglyceridemia by 20% to 50%. Eicosapentaenoic acid, EPA plus DHA, and icosapent ethyl, an ethyl ester product containing EPA without DHA, are approved by the US Food and Drug Administration for HTG > 500 mg/dL, at a dosage of 2000 mg twice daily. In the REDUCE-IT trial, adding icosapent ethyl, 2 g twice daily, to a statin in patients with HTG was associated with fewer ischemic events, compared to placebo.

Fish oil formulations can inhibit platelet aggregation and increase bleeding time in otherwise healthy people; however, such episodes are minor and nonfatal. Patients on anticoagulation or an antiplatelet medication should be monitored periodically for bleeding events, although recommendations on how to monitor aren’t specified in a recent advisory by the American Heart Association.

DHA was thought to increase the LDL-C levels and, by doing so, potentially counterbalance benefit, but most studies have failed to reproduce this effect. Instead, studies have shown minimal elevation of LDL-C when DHA is used to treat HTG.

**Niacin.** At a dosage of 500-2000 mg/dL, niacin lowers the TG level by 10% to 30%. It also increases HDL by 10% to 40% and lowers LDL by 5% to 20%.

**Considerations in pancreatitis.** For management of recurrent pancreatitis in patients with HTG, lifestyle modification remains the mainstay of treatment. When medication is considered for persistent severe HTG, fibrates have evidence of primary and secondary prevention of pancreatitis. When a patient is intolerant of fibrates, consider a different option to reduce the TG level—eg, fish oil supplementation.

**CASE 1**

**Recommendation for Mr. M: Therapeutic lifestyle changes to address moderate HTG.**

Because Mr. M’s 10-yr ASCVD risk is < 5%, statin therapy is not indicated for risk reduction. With a fasting TG value < 500 mg/dL, he is not considered at increased risk of pancreatitis.

**CASE 2**

**Recommendations for Ms. F:**

- **Therapeutic lifestyle changes to address severe HTG.** Ms. F agrees to wean off alcohol; add relaxation exercises before bedtime; do aerobic exercise 30 minutes a day, 3 times a week; decrease dietary carbohydrates daily by cutting portion size in half; and increase intake of fresh vegetables and lean protein.

- **Treatment with fenofibrate** to reduce the risk of pancreatitis. Ms. F begins a trial. Six months into treatment, she has reduced her BMI to 24 and the TG level has fallen to < 500 mg/dL. Ms. F also reports that she is sleeping well, believes that she is able to manage her infrequent anxiety, and is now in a routine that feels sustainable.

You congratulate Ms. F on her success and support her decision to undertake a trial of discontinuing fenofibrate, after shared decision-making about the risks and potential benefits of doing so.

**Summing up:**

**Management of HTG**

Keep these treatment strategy highlights in mind:

- Lifestyle modification with a low-fat, low-carbohydrate diet, avoidance of alcohol, and moderate-intensity exercise is the mainstay of HTG management.
- The latest evidence supports that HTG is a risk-enhancing factor for ASCVD and statin therapy is recommended for patients who have HTG and an ASCVD risk > 7.5%.
- When the TG level remains elevated despite statin therapy and lifestyle changes, an omega-3 ethyl ester can be used as an adjunct for additional atherogenic risk reduction.
- For severe HTG, a regimen of therapeutic lifestyle changes plus a fibrate is recommended to reduce the risk and recurrence of pancreatitis.

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